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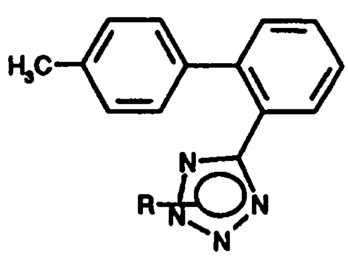
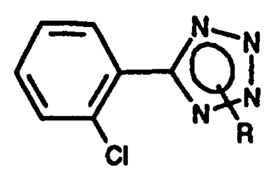


(I)



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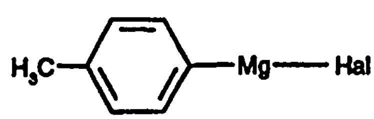

(III)

(57) Abstract

The invention relates to a process for the preparation of N-protected 4-methyl-2'--(5H-tetrazolyl)biphenyl of formula (I), in which R is a tetrazole protective group, wherein a compound of formula (II), in which R is a tetrazole protective group, is reacted with a compound of formula (III') in which Hal is halogen, in the presence of a transition metal catalyst, to novel compounds of formula (I) and their use, and to novel intermediates.

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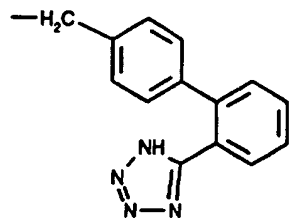
Process for the preparation of tetrazoles

The invention relates to a process for the preparation of N-protected 4-methyl-2'-(5H-tetrazolyl)biphenyl, to novel target compounds, and to novel starting compounds.

The novel substance class of angiotensin II antagonists opens up novel treatment methods, for example in the treatment of high blood pressure etc. Many of these compounds contain as structural element the 2'-(5H-tetrazolyl)-4-biphenylylmethylene group of the formula



5-(4'-Methylbiphenyl-4-yl)tetrazole and N-protected derivatives thereof are important building blocks in the synthesis of corresponding angiotensin II antagonists. Various efforts have been made to synthesize this structural element.

According to the EP Patent Application having the publication No. 253310 A2 or 324377 A2, the preparation proceeds, for example, from 4'-methyl-2-cyanobiphenyl only via a complicated multi-stage process.

U.S. Patent No. 5,039,814 discloses a route for the preparation, inter alia, of free or 2-tritylated 5-[(4'-methyl)biphenyl-4-yl]tetrazole. To this end, for example, 2-trityl-5-phenyltetrazole is first ortho-lithiated and then reacted with a 4-halotoluene by means of a transmetallation, if desired, the reaction advantageously being carried out in the presence of a catalyst. A disadvantage of this reaction is regarded to be the use of organolithium compounds, which can only be handled on a large scale using complicated safety precautions. Moreover, the use of these organolithium compounds clearly makes the production process more expensive, in particular when transmetallation takes place and the reaction is carried out in the presence of a phosphinated nickel or palladium catalyst. Furthermore, a protective group must not be used which has a hydrogen atom in the alpha-

positio:. to the tetrazole nitrogen atom, since this is preferably lithiated and thus the yield of this synthesis variant is clearly reduced.

The EP Patent Application having the publication No. 540356 A2 describes a Grignard reaction in which 5-(2-fluorophenyl)-1H-tetrazole is reacted with a phenylmagnesium halide, for example p-methylphenylmagnesium bromide. In this context, in many places the use and also the production and disposal of fluorine compounds is no longer appropriate for ecological reasons. Moreover, this synthesis requires approximately 3 equivalents of Grignard reagent; it must furthermore be carried out under reflux temperatures.

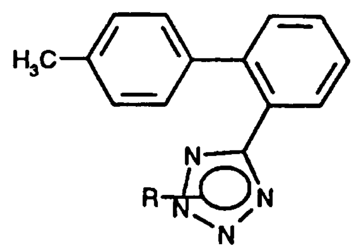
The European Patent Application having the publication No. 550313 A1 discloses, for example, a route for the preparation of N-protected 5-(4'-methylbiphenyl-2-yl)tetrazoles. In this process N-protected 2-iodophenyltetrazoles and 2-bromophenyltetrazoles are reacted with toluene derivatives metallated in position 4 by magnesium or zinc, or corresponding tolylboric acid compounds. The use of the bromine and iodine compounds concerned is not very suitable for large-scale use for reasons of cost. Moreover, the regeneration of the resulting bromides or iodides from waste waters is very complicated and cannot be justified for economic and ecological reasons. If appropriate zinc compounds or boric acid derivatives are used as organometallic compounds, provision likewise has to be made for a complicated separation of the metals from the waste waters. When using corresponding magnesium compounds, the yield obtained is unsatisfactory.

A further route for the preparation of 2-cyano-4'-methylbiphenyl via a Grignard reaction is revealed in the EP Patent Application having the publication No. 556468 A2. In this process, a 2-halobenzonitrile is treated with a 4-phenylmagnesium halide in the presence of a manganese salt. The formation of corresponding tetrazole derivatives starting from appropriate cyano compounds turns out to be complicated, since tetrazole formation often only takes place with tin azides (e.g. tributyltin azide) in relatively high yields for reasons of steric hindrance. Because of their high ecotoxicity, these azides can be handled on a large scale only with complicated safety precautions. In addition, the removal of tin compounds obtained as impurities from the final product proves very complicated.

The aim of the present invention consists in providing a novel synthesis for the preparation of N-protected 4-methyl-2'-(5H-tetrazolyl)biphenyl, which, independently of the nature of the

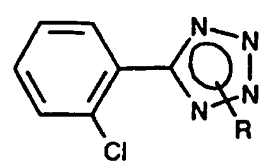
protective group, besides high yields does not have the disadvantages described above and moreover guarantees a minimization of the ecological pollution of the environment, is economically justifiable, and leads to largely isomerically pure target products and to products of high crystallizability.

It was possible to achieve this object by means of the present invention. The present invention relates to a process for the preparation of N-protected 4-methyl-2'-(5H-tetrazolyl)-biphenyl of the formula (I)

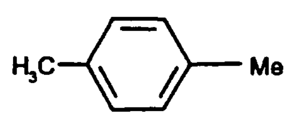


(I),

in which R is a tetrazole protective group,
wherein a compound of the formula (II)



in which R is a tetrazole protective group, is reacted with a compound of the formula (III)



in which Me is a metallic radical, in the presence of a transition metal catalyst.

The tetrazole protective group R should be stable to the organometal reagents used, adequately resistant to brominating agents (as in the next step or in one of the following steps in the reaction sequence for the preparation of angiotensin II antagonists a bromination is carried out) and also easy to introduce and easily removable. Suitable protective groups are, for example, lower alkyl, lower alkyl which (i) is monosubstituted or

polysubstited by aryl, or (ii) is substituted by aryl-lower alkoxy, lower alkoxy or lower alkylthio, 2-tetrahydropyranyl, allyl and silyl. Aryl is, for example, phenyl or pyridyl, each of which, independently of one another, is unsubstituted or monosubstituted or polysubstituted, e.g. di- or trisubstituted, e.g. by lower alkyl or lower alkoxy. Silyl is, for example, tri-lower alkylsilyl. Examples of appropriate protective groups which may be mentioned are tert-butyl, benzyl, p-methoxybenzyl, 2-phenyl-2-propyl, diphenylmethyl, di(p-methoxyphenyl)methyl, trityl, (p-methoxyphenyl)diphenylmethyl, diphenyl(4-pyridyl)methyl, benzyloxymethyl, methoxymethyl, ethoxymethyl, methylthiomethyl, 2-tetrahydropyranyl, allyl and tri(m)ethylsilyl.

Preferred protective groups are, for example, benzyl, p-methoxybenzyl and diphenylmethyl; 2-phenyl-2-propyl is particularly preferred.

The protective group R is localized in the 1-position or preferably in the 2-position of the tetrazole ring.

A metallic radical Me is, for example, -Mg-Hal, Hal being halogen, such as chlorine, bromine or iodine. Hal is preferably bromine.

Suitable transition metal catalysts are, for example, corresponding manganese, cobalt, palladium and, primarily, nickel catalysts, such as nickel(II) halide, e.g. chloride, or nickel acetylacetonate, preferably in the presence of a complexing agent, such as a phosphine, e.g. triphenylphosphine. The catalyst (in particular an Ni salt) is advantageously pretreated with a reducing agent, such as a hydride which, if desired, is complex, e.g. dibutylaluminium hydride or diisobutylaluminium hydride, or a methylmagnesium halide, e.g. methylmagnesium chloride, corresponding Ni(0) catalysts, such as $Ni[P(C_6H_5)_3]_4$, resulting. Preferably, systems comprising nickel acetylacetonate, triphenylphosphine and diisobutylaluminium hydride are used. Advantageously, 1 to 10 mol %, primarily 2 to 7 mol %, of catalyst are employed per mole of compound of the formula (II).

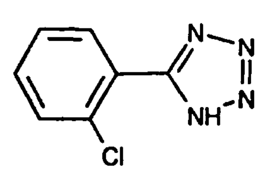
The phenyl-phenyl coupling according to the invention is carried out, for example, in an inert solvent in a temperature range from approximately 0°C up to the boiling point of the solvent or solvent mixture, e.g. approximately between 20°C and approximately 80°C. Suitable inert solvents are, for example, aliphatic or aromatic hydrocarbons, such as a lower alkyl

benzene, or ethers, such as cyclic ethers, e.g. hexane, toluene, a xylene, dioxane or tetrahydrofuran, or mixtures thereof. A molar ratio of compound (II) to compound (III) is, for example, approximately 1.5 to approximately 0.25, primarily approximately 1.0 to approximately 0.5.

Advantageously, the reaction is carried out in an aromatic hydrocarbon, such as a lower alkyl benzene, e.g. toluene or a xylene, an ether, such as a cyclic ether, e.g. tetrahydrofuran, or a mixture thereof. Particularly advantageously, the reaction according to the invention proceeds in a mixture of lower alkyl benzene, in particular toluene or a xylene, and a cyclic ether, in particular tetrahydrofuran. Advantageously, 0.5 to 3 litres, primarily 1 to 2 litres, of solvent are employed per mole of compound of the formula (II).

It is known to prepare biaryls in the presence of transition metal catalysts starting from aryl halides and metallated aryls. It is furthermore known that appropriate bromides or iodides are employed as aryl halides, since halides of this type have a better reactivity compared with corresponding chlorides. If, for example, the reaction conditions as are described in EP 550313 A1 are applied to starting substances of the formulae (II) and (III), significantly lower yields are obtained than when using the inventive conditions of the present process. All the more surprising is the finding that the inventive use of compounds of the formula (II) leads to higher yields of products of the formula (I), compared with the methodology according to EP 550313, in which corresponding iodine derivatives were employed.

The compounds of the formula (II) can be prepared by introduction of the protective group R into the compound of the formula (IV)



or a proton tautomer thereof.

The compound of the formula (IV) can exist as proton tautomers. The hydrogen atom of the tetrazole ring can be bonded to different N atoms of this ring. Corresponding tautomers are in equilibrium with one another.

If activated alcohols of the type R-OH (V), e.g. compounds of the formula R-X (Va) in which X is halogen or sulfonyloxy, e.g. methanesulfonyloxy, are employed as reagents for the introduction of the protective group, the reaction can be carried out in the presence of a base. Tetrazoles of the formula (IV) are particularly preferably reacted with alcohols of the formula (V) in the presence of an acid.

Possible bases are, for example, alkali metal hydroxides, hydrides, amides, alkoxides, carbonates, triphenylmethylides, di-lower alkylamides, aminoalkylamides or lower alkylsilylamides, naphthalenamines, lower alkylamines, basic heterocycles, ammonium hydroxides, and also carbocyclic amines. Examples which may be mentioned are sodium hydroxide, hydride or amide, sodium (m)ethoxide, potassium tert-butoxide or carbonate, lithium triphenylmethylide or diisopropylamide, potassium 3-aminopropylamide or bis(trimethylsilyl)amide, dimethylaminonaphthalene, di- or triethylamine, or ethyldiisopropylamine, N-methylpiperidine, pyridine, benzyltrimethylammonium hydroxide, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Suitable acids are, for example, inorganic acids, such as mineral acids, e.g. sulfuric acid, a phosphorus or halohydric acid, or organic acids. Organic sulfonic acids are preferred, such as unsubstituted or substituted, e.g. by halogen, [(C_1-C_4)-]alkane or arylsulfonic acids e.g. methane- or toluenesulfonic acid.

If acids are employed in the reaction of the compound of the formula (IV) with compounds of the formula (V), the protective group R is surprisingly preferably bonded in position 2 of the tetrazole ring, while, in contrast, when using bases, the protective group is bonded both in position 1 and in position 2. The use of acids unexpectedly causes the formation of an essentially isomerically pure form. The choice of the condensing agent thus plays a significant part for the synthesis of an essentially isomerically pure form. For example, products having an isomeric purity of more than 75%, advantageously of more than 90%, are thus obtained.

The protective group can also be introduced by addition of a corresponding olefinic derivative derived from the alcohol of the formula (V). For example, the 2-pyranyl protective group is thus introduced by acid-catalysed reaction with dihydropyran, and the 2-phenyl-

2-propyl group by reaction with 2-phenylpropene. Accordingly, the present invention also relates to the preparation of compounds of the formula (IV) shown above.

The invention furthermore relates to the following process sequence for the preparation of compounds of the formula (I), wherein
(a) a protective group R is introduced into the compound of the formula (IV) or a proton tautomer thereof and then
(b) a resultant compound of the formula (II) is reacted with a compound of the formula (III) in which Me is a metallic radical, in the presence of a transition metal catalyst.

The present invention further relates to new compounds of the formula (I) and new starting materials which can be used for the preparation of compounds of the formula (I), i.e. in particular new compounds of the formulae (II) and (IV), and the use of compounds of the formulae (II) and (IV) for the preparation of compounds of the formulae (I) and also for the preparation of angiotensin (II) antagonists which contain the 2'-(5H-tetrazolyl)-4-biphenylylmethylene group. The methyl group in compounds of the formula (I) can thus be halogenated by treatment with a halogenating reagent. For example, the methyl group can be brominated, a customary brominating agent being employed, e.g. N-bromosuccinimide, advantageously in the presence of an azo compound, e.g. azobisisobutyronitrile. The preparation of angiotensin (II) antagonists of this type is described, for example, in the European Patent Application having the publication No. 253310.

A further preferred subject of the present invention are the following compounds:
5-[2-(4'-methylbiphenylyl)]-2-[(2-phenyl)-2-propyl]tetrazole;
5-[2-(4'-methylbiphenylyl)]-2-(diphenylmethyl)tetrazole;
5-[2-(4'-methylbiphenylyl)]-2-(4-methoxybenzyl)tetrazole;
5-(2-chlorophenyl)-2-[(2-phenyl)-2-propyl]tetrazole;
5-(2-chlorophenyl)-2-(diphenylmethyl)tetrazole;
5-(2-chlorophenyl)-2-(4-methoxybenzyl)tetrazole.

The following examples serve to illustrate the present invention, but should in no way restrict this.

Example 1: 5(-2-Chlorophenyl)-2-(4-methoxybenzyl)tetrazole

2 ml of methanesulfonic acid are added to a suspension of 36 g of 5-(2-chlorophenyl)-tetrazole in 150 ml of toluene and a solution of 28 g of 4-methoxybenzyl alcohol in 60 ml of toluene is added dropwise at a temperature of approximately 110°C with azeotropic separation of water. The solution is additionally stirred for about 10 minutes, then cooled to room temperature, diluted with 100 ml of toluene, washed, first with water then with a solution of sodium hydrogen carbonate, and concentrated to dryness. According to the NMR spectrum, the crude product (yield 61 g; 100% of theory) contains about 90% of 5-(2-chlorophenyl)-2-(4-methoxybenzyl)tetrazole and about 10% of the 1-(4-methoxybenzyl) isomer. After recrystallization from isopropanol, 51.2 g (85 % of theory) of the isomer-free 5-(2-chlorophenyl)-2-(4-methoxybenzyl)tetrazole are obtained, m.p.. 77-79°C (uncorrected).

The following can be prepared, for example, in an analogous manner:

(a) 5-(2-Chlorophenyl)-2-benzyltetrazole (crude yield about 100% of theory)

According to the NMR spectrum, the crude product contains about 75% of the 2-benzyl isomer and about 25% of the 1-benzyl isomer. Oil, crystallizes on allowing to stand. [thin-layer chromatography (TLC); silica gel plate; mobile phase: hexane/ethyl acetate 2:1; $R_f = 0.28$ (1-benzyl isomer); $R_f = 0.5$ (2-benzyl isomer)]

(b) 5-(2-Chlorophenyl)-2-[(2-phenyl)-2-propyl]tetrazole

Yield about 100%, oily, isomerically pure according to TLC [silica gel plate, mobile phase: hexane/ethyl acetate 2:1; R_f: about 0.66]

(c) 5-(2-Chlorophenyl)-2-(diphenylmethyl)tetrazole

Crude yield about 100%, oily, isomerically pure according to TLC [mobile phase: hexane/ethyl acetate 2:1; R_f: about 0.59].

Example 2: 5-(2-Chlorophenyl)-1-benzyltetrazole and 5-(2-chlorophenyl)-2-benzyltetrazole

10.6 g of benzyl bromide is added dropwise at a temperature of about 60°C to a well-stirred mixture of 9 g of 5-(2-chlorophenyl)tetrazole, 30 ml of toluene, 0.4 g of tetrabutylammonium hydrogen sulfate and 30 g of 2N aqueous sodium hydroxide solution. The solution is additionally stirred for about 1 hour, then cooled to room temperature, and the toluene phase is separated off, washed with dilute sodium hydroxide solution in water and

evaporated to dryness. According to the NMR spectrum, the crude product (11.1 g; 82% of theory) contains about 40% of the 2-benzyl isomer and about 60% of the 1-benzyl isomer. Oil, crystallizes on allowing to stand. Thin-layer chromatography [silica gel plate; mobile phase: hexane/ethyl acetate 2:1; R_f = 0.28 (1-benzyl isomer); R_f = 0.5 (2-benzyl isomer)]

Example 3: 5-(2-Chlorophenyl)-2-[(2-phenyl)-2-propyl]tetrazole

1 ml of methanesulfonic acid is added to a suspension of 18 g of 5-(2-chlorophenyl)tetrazole in 150 ml of toluene and a solution of 12.2 g of 2-phenylpropene in 30 ml of toluene is added dropwise at a temperature of approximately 110°C. The solution is additionally stirred for about 10 minutes, then cooled to room temperature, diluted with 100 ml of toluene, washed, first with water then with a solution of sodium hydrogen carbonate, and concentrated to dryness. The crude product (yield 27.5 g; 92% of theory) is oily and isomerically pure according to thin-layer chromatography (cf. Example 1b).

Example 4: 5-[2-(4'-Methylbiphenylyl)]-2-(4-methoxybenzyl)tetrazole

A solution of 4-tolylmagnesium bromide is prepared at 60°C from 7 g of magnesium in 50 ml of tetrahydrofuran and 44.6 g of 4-bromotoluene in 90 ml of toluene. 49 g of 5-(2-chlorophenyl)-2-(4-methoxybenzyl)tetrazole at 20-30°C are added to a mixture of 50 ml of toluene, 2.3 g of nickel acetylacetonate, 8.8 g of triphenylphosphine and 17.5 ml of an about 20 % solution of diisobutylaluminium hydride in toluene and subsequently the 4-tolylmagnesium bromide solution prepared above is added dropwise, then the mixture is additionally stirred for about 20 hours. 175 ml of toluene and 175 ml of 2N hydrochloric acid are then added, and the toluene phase is separated off and concentrated. The evaporation residue is crystallized from isopropanol. Yield: 45 g, 78% of theory; m.p. 75-77°C. A further 3.9 g (7% of theory) of the product can be obtained from the mother liquor by chromatography on silica gel. Total yield: 85% of theory.

The following can be prepared, for example, in an analogous manner:

(a) 5-[2-(4'-Methylbiphenylyl)]-2-benzyltetrazole

Starting from crude 5-(2-chlorophenyl)-2-benzyltetrazole. Crude yield about 100%. [TLC; silica gel plate; mobile phase: hexane/ethyl acetate 2:1; R_f = 0.2 (1-benzyl isomer); R_f = 0.38 (2-benzyl isomer)].

According to the NMR spectrum, the crude product contains about 75% of the 2-benzyl isomer and about 25% of the 1-benzyl isomer.

(b) 5-[2-(4'-Methylbiphenylyl)]-2-[(2-phenyl)-2-propyl]tetrazole starting from 5-(2-chlorophenyl)-2-[(2-phenyl)-2-propyl]tetrazole.

Yield: 79% of theory; m.p. 102-103 (uncorr.)

(c) 5-[2-(4'-Methylbiphenylyl)]-2-(diphenylmethyl)tetrazole starting from 5-(2-chlorophenyl)-2-diphenylmethyltetrazole.

Crude yield about 100%; TLC; silica gel plate; mobile phase: toluene; R_f = 0.3.

Example 5: 5-[2-(4'-Methylbiphenylyl)]-2-(2-phenyl-2-propyl)tetrazole

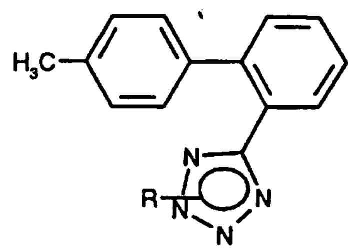
A solution of 4-tolylmagnesium bromide is prepared at 60° from 21.6 g of magnesium in 170 ml of tetrahydrofuran and 135.5 g of 4-bromotoluene in 300 ml of toluene.

1 54.3 g of 5-(2-chlorophenyl)-2-(2-phenyl-2-propyl)tetrazole at 20-30° are added to a mixture of 180 ml of toluene, 6.8 g of nickel acetylacetonate, 26.4 g of triphenylphosphine and 54 ml of a solution of diisobutylaluminium hydride in toluene and subsequently the 4-tolyl-magnesium bromide solution prepared above is added dropwise. The mixture is then additionally stirred for about 20 hours. 480 ml of toluene and 480 ml of 2N hydrochloric acid are added and the toluene phase is separated off and concentrated in vacuo. The evaporation residue is crystallized from isopropanol. 5-[2-(4'-Methylbiphenylyl)]-2-(2-phenyl-2-propyl)tetrazole is thus obtained.

Yield (without working up the mother liquor): 162.8 g (83.5% of theory); m.p. 102-103°.

WHAT IS CLAIMED IS:

1. A process for the preparation of N-protected 4-methyl-2'-(5H-tetrazolyl)biphenyl of the formula (I)

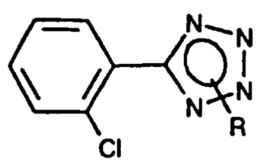


(I),

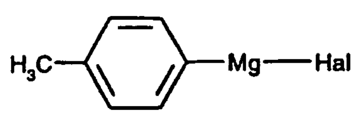
in which R is a tetrazole protective group,

wherein

a compound of the formula (II)



in which R is a tetrazole protective group, is reacted with a compound of the formula (III')



in which Hal is halogen, in the presence of a transition metal catalyst.

2. A process according to claim 1, wherein the transition metal catalysts employed are manganese, cobalt, palladium or nickel catalysts.

3. A process according to claim 2, wherein the transition metal catalyst employed is a nickel catalyst.

4. A process according to claim 3, wherein an Ni salt is pretreated with a reducing agent, such as a hydride which, if desired, is complex, e.g. di(iso)butylaluminium hydride, or a

methylmagnesium halide, e.g. methylmagnesium chloride, and employed in the presence of a complexing agent, such as a phosphine, e.g. triphenylphosphine.

5. A process according to any one of claims 1-4, wherein 1 to 10 mol %, in particular 2 to 7 mol %, of catalyst are employed per mole of compound of the formula (II).

6. A process according to any one of claims 1-5, wherein the reaction is carried out in a lower alkylbenzene, such as toluene or a xylene, or a cyclic ether, such as tetrahydrofuran, as a solvent or a mixture thereof.

7. A process according to claim 6, wherein the reaction is carried out in a mixture of toluene and tetrahydrofuran.

8. A process according to claim 7, wherein 0.5 to 3 litres, in particular 1 to 2 litres, of solvent are employed per mole of compound of the formula (II).

9. A process according to any one of claims 1-8, wherein a possible protective group R is lower alkyl, lower alkyl which (i) is monosubstituted or polysubstituted by aryl, or (ii) is substituted by aryl-lower alkoxy, lower alkoxy or lower alkylthio, 2-tetrahydropyranyl, allyl or silyl.

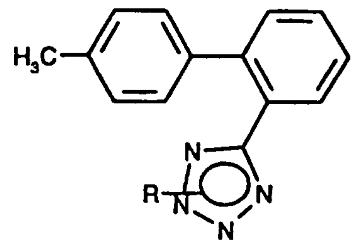
10. A process according to claim 9, wherein a possible protective group R is tert-butyl, benzyl, p-methoxybenzyl, 2-phenyl-2-propyl, diphenylmethyl, di(p-methoxyphenyl)methyl, trityl, (p-methoxyphenyl)diphenylmethyl, diphenyl(4-pyridyl)methyl, benzyloxymethyl, methoxymethyl, ethoxymethyl, methylthiomethyl, 2-tetrahydropyranyl, allyl or tri(m)ethylsilyl.

11. A process according to claim 10, wherein a possible protective group R is benzyl, p-methoxybenzyl, diphenylmethyl or 2-phenyl-2-propyl.

12. A process according to any one of claims 1-11, wherein the protective group R is localized in the 1-position or preferably in the 2-position of the tetrazole ring.

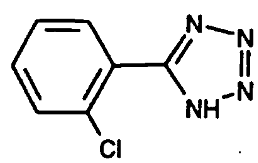
13. A process according to any one of claims 1-12, wherein the starting material used is a compound of the formula (III) in which Hal is bromine.

14. A process for the preparation of N-protected 4-methyl-2'-(5H-tetrazolyl)biphenyl of the formula (I)

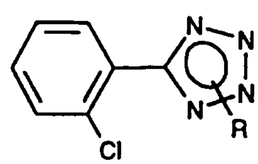


(I),

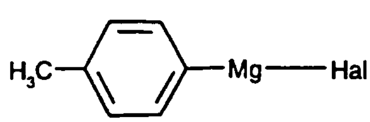
in which R is a tetrazole protective group,
wherein
(a) the protective group R is introduced into the compound of the formula (IV)



or a proton tautomer thereof and
(b) a resultant compound of the formula (II)



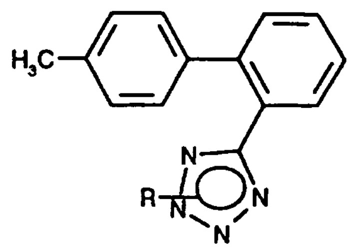
in which R is a tetrazole protective group, is reacted with a compound of the formula (III')



in which Hal is halogen, in the presence of a transition metal catalyst.

15. A process according to claim 14, wherein the starting material is a compound of the formula (IV) and this is reacted with 2-phenylpropene in the presence of an acid to give a compound of the formula (II) in which R is 2-phenyl-2-propyl.

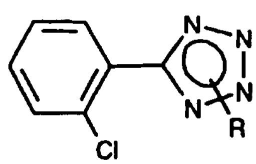
16. N-protected 4-methyl-2'-(5H-tetrazolyl)biphenyl of the formula (I)



(I),

in which R is benzyl, p-methoxybenzyl, diphenylmethyl or 2-phenyl-2-propyl.

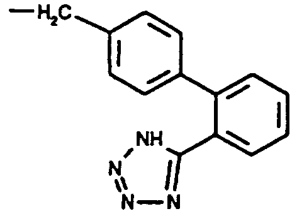
17. A compound of the formula (II)



in which R is benzyl, p-methoxybenzyl, diphenylmethyl or 2-phenyl-2-propyl.

18. A compound selected from:
5-[2-(4'-methylbiphenylyl)]-2-[(2-phenyl)-2-propyl]tetrazole;
5-[2-(4'-methylbiphenylyl)]-2-(diphenylmethyl)tetrazole;
5-[2-(4'-methylbiphenylyl)]-2-(4-methoxybenzyl)tetrazole;
5-(2-chlorophenyl)-2-[(2-phenyl)-2-propyl]tetrazole;
5-(2-chlorophenyl)-2-(diphenylmethyl)tetrazole, and
5-(2-chlorophenyl)-2-(4-methoxybenzyl)tetrazole.

19. The use of a compound of the formula (I) in which R is a tetrazole protective group, such as benzyl, p-methoxybenzyl, diphenylmethyl or 2-phenyl-2-propyl, for the preparation of an angiotensin (II) antagonist which as structural element contains the 2'-(5H-tetrazolyl)-4-biphenylyl methylene group of the formula



INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/EP 95/04143

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D257/04 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	DE,A,43 13 747 (BAYER AG) 3 November 1994 see claim 1 ---	1-19
X	EP,A,0 540 356 (ORTHO PHARMACEUTICAL CORP) 5 May 1993 cited in the application see claim 1 ---	1-19
X	EP,A,0 550 313 (SYTHELAB) 7 July 1993 cited in the application see claim 7 -----	1-19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
23 January 1996	16.02.96

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Internal ' Application No
PCT/EP 95/04143

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		AU-B-	2740492	06-05-93
		CA-A-	2081847	02-05-93
		JP-A-	5279350	26-10-93
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		US-A-	5371233	06-12-94